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## DISCUSSION

**Brig. T. E. Osmond,** the President, said that although he thought it was more effective to wait three weeks before employing pyretotherapy, this delay was inexpedient for gonorrhoeal cases in the Army. It was necessary to resort to this form of treatment for soldiers as soon as drug resistance became evident in order to get them back to duty as soon as possible. Fever produced by vaccine injections gave good results in some cases but brilliant ones had been obtained with the Kettering Hypertherm. He understood from his colleagues in the United States Army that penicillin had been used with success in over 90 per cent of drug-resistant gonococcal infections.

Dr. **H. M. Hanschell** said that an innate resistance of the gonococcus to the sulphonamides was a rare characteristic. The careful clinical and bacteriological observations made by Dr. Harkness had shown that some factor in the host played a part in the resistance of the infection. Although there was as yet no supporting experimental evidence, the suggestion that the sulphonamides might prevent the development of immune antibodies was an important one. The metabolites which were rendered unusable by the gonococcus were also needed by the tissue cells but presumably their utilization by these tissue cells was also hindered. Although nearly all the early cases of gonococcal infection responded promptly to treatment there were occasional failures. Clinical experience of the failures had shown that after omission of the sulphonamide treatment for a period of five or six weeks, the same dosage of the sulphonamide was often rapidly successful. Presumably antibody formation had been delayed until, at last, it became present in sufficient quantity to provide effective support to the sulphonamide treatment. When considered from the public health aspect evidently it was unwise to use the beneficial effect of this time factor for ambulant patients who were carrying a contagious disease; there should not be any delay in the employment of the sulphonamide drugs. The late Prof. Yorke and his colleagues had shown, as Dr. Harkness had reminded them, that resistant strains of trypanosomes, unlike the susceptible strains, failed to absorb arsenical compounds. This chemotherapeutic action differed from that

of the sulphonamides, which was a blockage of the enzyme-metabolite system. A combined attack on the gonococcus with both types of chemotherapy would be of great value. We knew that neoarsphenamine was bactericidal to various organisms—anthrax, some strains of non-haemolytic streptococcus and certain puerperal streptococcal infections ; presumably the action on these bacteria of neoarsphenamine was similar to that on trypanosomes. An agent possessing this type of action against the gonococcus when used together with a sulphonamide would produce a dual therapy of high value. The use of propamidine in five cases of gonococcal urethritis had given encouraging results. The five patients concerned, who had all proved resistant to several courses of sulphathiazole, were treated with an additional course of this sulphonamide during which two intravenous injections, each of 0·25 centigram, of propamidine were given ; four of the patients treated with this dual therapy were cured. It was unlikely, however, that this drug which produced an alarming fall in blood pressure would come into general use, except in kala-azar and African sleeping sickness which so often proved fatal.

Wg. cdr. **G. L. M. McElligott** said that he was pleased to hear Dr. Harkness emphasize the value of the time factor in the cure of gonorrhoea. There was a tendency at the end of a difficult case for venereologists to take credit for a cure which rightly belonged to the patient's own capacity to manufacture antibodies. This was especially true in cases in which many kinds of treatment had been tried. With regard to the theory that the sulphonamide drugs might have a deleterious effect on antibody formation, he felt that this effect might equally well prove to be on the antigen, that is on the gonococcus, rather than on the antibody. Particularly " knocked out " gonococci would be second-rate antigens. The gonococcus always recovered up to a point, but did it ever do so completely within a reasonable time ? Very acute relapses were uncommon after chemotherapy ; the inflammatory response was usually subacute. Generally the disease at once settled down into a subacute form. He did not share Dr. Harkness's belief in the completely resistant case ; in his experience and that of his co-workers, cases in which the gonococcus did not partially respond to adequate sulphonamide chemotherapy were very uncommon.

Dr. **Mascall** agreed that there seemed to be too much impetuosity in treating venereal disease. At the present time a patient diagnosed as suffering from gonorrhoea was immediately given the shortest course of a sulphonamide. If he did not react promptly, some form of fever therapy, often of considerable risk to the patient, was instituted. Then the patient was obliged to return to his unit or to his work without a proper test or period of observation. In many instances he returned later with a recurrence of the discharge which was diagnosed as " non-specific urethritis " but which was due, in reality, to the original gonococcal infection. There was a tendency to neglect the ordinary routine investigation which formerly was carried out. In many clinics today the prostate was not examined, and he was still convinced that in many cases it was the source of considerable trouble even after the efficient use of the sulphonamides. The gonococcal fixation test had become unpopular with some people who had difficulty in appreciating its clinical significance. In the very early stages of the infection the sulphonamides undoubtedly killed gonococci before antibodies could be formed ; the test then remained negative. There was also the patient whose gonococcal fixation test remained persistently positive in the absence of symptoms, and he considered this to be an indication that the treatment had turned the patient into a " carrier," with a focus locked up somewhere in the tissues. This carrier state, particularly in the case of vulvo-vaginitis in children, constituted a worrying problem. He had seen a child who had remained free from symptoms for periods of six to nine months, yet in spite of this quiescence, tests proved that gonococci were still present. This could happen in adults also and Dr. Mascall thought that this dormant state accounted for many of the relapses after sulphonamide treatment. Treated male patients sometimes returned with a strongly positive gonococcal fixation test, complaining of an early morning discharge or showing a few threads in the urine ; the prostatic secretion contained twenty pus cells per high power field. He had noted that prostatic massage gradually cleared up the symptoms but these cases needed much patience and prolonged treatment. He had used intravenous injections of sulphamezathine and had obtained a high blood concentration, but relapses still occurred. He agreed with Dr. Harkness that there must be a host factor in connexion with drug resistance. In civilian practice there were not enough facilities for fever treatment ; hospital bed accommodation was very restricted.

Dr. **C. Hamilton Wilkie** said that he agreed thoroughly with what Dr. Harkness had said regarding the gonococcal fixation test. He would like to know what reliance Dr. Harkness placed in this.

Dr. **Harkness** replied that he thought it was useless.

Dr. **G. Brownlee** said that the drug concentrations were too high in the first series of tests carried out for Dr. Harkness. They in the laboratory were interested in following these cases from the point of view of susceptibility or resistance. In the past they had felt that, with an adequate blood level, susceptibility or resistance was primarily an enzyme process. He himself was now concerned to think otherwise as he considered that Dr. Harkness had proved his case. One could however be misled to a degree, because there must be circulating gonococci of all orders of resistance by reason of passage. It was rather like solving an equation with a number of unknown quantities and he would add that note of caution in coming to any conclusion at this stage. The reference to other drugs which might not have combative enzyme systems appeared to the pharmacologist to be a hopeless question. Was a word of caution out of place about penicillin treatment where one believed that resistant types would be found ? In any system which postulated interference with an enzyme there would doubtless be degrees of resistance to the system.

Maj. **Marjorie Bolton** stated that the choice of the continuation treatment of these partially drug-resistant cases presented a difficult problem. Was it desirable to try the effect of an average course of treatment with several sulphonamides, or was it more suitable to give larger amounts of one of these compounds in order to obtain a higher concentration in the blood ? It was by no means a simple matter to decide when these cases should be classified as drug-resistant.

Dr. **R. Marinkovitch** asked Dr. Harkness whether there was any predominance of sex in the resistant cases. In his experience the majority of infections in women became partially resistant. In treating men he combined urethrovesical irrigations with chemotherapy and gave two tablets of sulphathiazole four times a day for five days. The irrigations were carried out for from two to four weeks. As soon as the urine became clear prostatic massage was done as a routine. He had not found the so-called true resistance to sulphathiazole.

Dr. **R. Forgan** said that he did not propose to follow Dr. Hanschell into the realms of clinical experiment which he had bravely entered, but he wished to refer to the fact that in America it had been possible to test the value of penicillin in cases of gonorrhoea resistant to sulphonamides. He thought it was not right that venereologists in Great Britain should be at a disadvantage compared with their colleagues in America in respect of a new chemical substance which, after all, had its origin in England. The Society was fortunate in having present the chief advisers on venereal diseases to the Navy, Army and Air Force. He suggested that the meeting should ask them to bring pressure on the authorities to release penicillin for experimental use by Dr. Harkness and other leading British venereologists.

Dr. **F. C. Doble** pointed out that some persistent infections responded to the injection of 5 to 15 cubic centimetres of whole blood. He quoted a case of stricture with repeated relapses of urethral discharge which illustrated the efficacy of this measure.

Col. **L. W. Harrison** (who was unable to be present), sent the following note.

" In case nobody taking part in the discussion has referred to some recent work by Kimmig, perhaps the following note may be interesting, as it is evidence that sulphonamide resistance is not likely to be acquired by under-dosage, as so many of us have feared, but is a natural attribute of certain strains of gonococci—perhaps because they have no appetite for sulphonamides. J. Kimmig (*Klin. Wschr.*, 1943, **22,** 31) trained four strains of gonococci which were normally sensitive to sulphonamides to become resistant *in vitro*, so that they were then able to grow in a concentration of 1 in 60,000. At this stage they were inoculated into human urethras but in repeated trials completely failed to infect. In contrast, the parent strains of two of these artificially resistant strains were found to be still virulent when they were in their seventieth subculture, showing that the loss of virulence in the sulphonamide-resistant offspring was not due to age in culture. All attempts to revive the virulence of these artificially resistant strains failed. Kimmig isolated from sulphonamide-resistant cases of gonorrhoea eight strains, of which five were able to grow in medium containing concentrations of sulphonamide as strong as 1 in 2,000 and three in a concentration of 1 in 20,000. I suggest that the explanation is that they had no appetite for the sulphonamide so that it was unable to bring about their starvation."

Dr. **Harkness**, in reply, said he did not consider that the incidence of drug resistance was higher in the female than in the male. The female was more liable to develop closed foci of infection which were often resistant to the sulphonamides, and surgical interference might be necessary. The treatment for drug resistance, partial or complete, was the same ; the best method for observing progress was to make an examination before the first morning micturition. He agreed with Wg. cdr. McElligott that complete and partial drug resistance were not always clear-cut entities, but he could not understand why Wg. cdr. McElligott had not observed the persistence of profuse gonococcal discharges when the resistance was complete : this was much more frequent than partial resistance. In reply to Dr. Marinkovitch he considered that the posterior urethra was always involved in these cases and that sulphathiazole was the drug of choice. Dr. Marinkovitch had made an interesting observation concerning the incidence of residual infections due to non-specific organisms. These cases were mostly due to a faulty technique in irrigation but they sometimes occurred in clinics where urethrovesical irrigations were not prescribed until a diagnosis of drug resistance had been made. Dr. Harkness considered that the primary infection in these cases was caused by the gonococcus and one or more non-specific organisms. Dr. Hanschell had made an interesting observation about intravenous injections of propamidine. He, Dr. Harkness, was also trying *p*-chloro-xylenol in 70 per cent solution of methyl acetamide (as recommended by Zondeck and Bromberg) and the sodium salts of pentose nucleotides. He had not yet observed the effects of these drugs on a sufficient number of cases to form a definite opinion on their efficacy.

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**The Wassermann reaction**

The problem of carrying out the Wassermann reaction without the guinea-pig complement has been solved by the serological laboratory of the Leningrad Institute for Blood Transfusion. Fresh blood serum is substituted ; in about 70 per cent of cases active complement occurs in human blood. Some 50,000 tests have already been made by means of the new method and they prove that it is possible to employ the human complement when carrying out the Wassermann reaction. The remnants of the sera of the preceding experiments have now been found to be usable. This method reduces the cost and simplifies the procedure of carrying out this reaction.—*U.S.S.R. Society for cultural relations with other countries, Medical Chronicle*, January, 1944.